Correction of cerebellar movement related deficits by normalizing Dyrk1a copy number in the Ts65Dn mouse model for Down syndrome

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Elucidation of the underlying mechanisms involved in brain related deficits of Down syndrome (DS) would be useful for consideration of therapeutic interventions. Several DS-specific phenotypes have been hypothesized to be linked to altered expression or function of specific trisomic genes. One such gene of interest is *DYRK1A*, which has been implicated in behavioral functions of the hippocampus and cerebellum. The Ts65Dn mouse model for DS includes a triplication of *Dyrk1a* in addition to a triplication of >100 other human chromosome 21 mouse orthologs. To evaluate the role of *Dyrk1a* in cerebellar function, we have genetically normalized the *Dyrk1a* copy number in otherwise trisomicTs65Dn mice and reduced *Dyrk1a* copy number in otherwise euploid mice (2N) for a total of 3 alternative genetic doses of *Dyrk1a:* Euploid-*Dyrk1a*$^{+/+}$, Euploid-*Dyrk1a*$^{+/-}$, Ts65Dn-*Dyrk1a*$^{+/+/+}$, and Ts65Dn-*Dyrk1a*$^{+/+/-}$. Cerebellar movement-related function in these knockdown models is being assessed through a novel behavioral balance beam task. Additionally, levels of *Dyrk1a* activity in the cerebellum for all genotypes were analyzed by HPLC. We have previously demonstrated that Ts65Dn-*Dyrk1a*$^{+/+/+}$ mice perform worse in the balance beam task in comparison to Euploid-*Dyrk1a*$^{+/+}$ mice. Preliminary results of the current study do not indicate such a difference among Ts65Dn-*Dyrk1a*$^{+/+/+}$ mice in comparison to Euploid-*Dyrk1a*$^{+/+}$ mice. We hypothesize that the lack of replication of the previous findings may be due to differences in postweaning housing environments. Mice in the previous study were single-housed, whereas mice in the present study were group-housed, which may help mitigate motor deficits in the trisomic mice. Additionally, current trends display a deficit in balance beam performance of both the Euploid-*Dyrk1a*$^{+/-}$ and the Ts65Dn-*Dyrk1a*$^{+/+/-}$ groups, which suggests that reducing the copy number of *Dyrk1a* by one may have detrimental effects on motor coordination. Concomitant analysis of the balance beam performances and Dyrk1a activity levels may indicate the sensitivity of the balance beam task to assess the role Dyrk1a activity in cerebellar function.

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